In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: April 30, 2020

MICHELLE GREEN,	*	PUBLISHED
Petitioner,	*	No. 16-008V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Influenza; Asthma; Significant Aggravation; IgE; Allergy; Hypersensitivity Reaction.
Respondent.	*	

Lawrence R. Cohan & David Carney, Anapol Weiss, Philadelphia, PA, for petitioner.[1]
Ryan D. Pyles, U.S. Department of Justice, Washington, DC, for respondent.

DECISION ON ENTITLEMENT[2]

On January 4, 2016, Michelle Green ("petitioner") filed a timely petition in the National Vaccine Injury Compensation Program.[3] Petition (ECF No. 1). Petitioner alleged that an inactivated trivalent influenza ("flu") vaccination on September 15, 2014, caused the significant aggravation of her pre-existing asthma with the first manifestation of symptoms five days later. *Id.* After fully reviewing all of the evidence and testimony presented in this case in accordance with the applicable legal standards, I find that petitioner has not met her legal burden of

[1] Mr. Cohan is the attorney of record; Mr. Carney presented petitioner's case at the entitlement hearing.

[2] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), because this decision contains a reasoned explanation for the action in this case, I am required to post it on the website of the United States Court of Federal Claims. The court's website is at http://www.uscfc.uscourts.gov/aggregator/sources/7. **This means the decision will be available to anyone with access to the Internet.** Before the decision is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). "An objecting party must provide the court with a proposed redacted version of the decision." *Id.* **If neither party files a motion for redaction within 14 days, the decision will be posted on the court's website without any changes.** *Id.*

[3] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-1 to 34 (2012) ("Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

establishing that the vaccination significantly aggravated her pre-existing condition. Accordingly, petitioner is not entitled to compensation. [4]

I. Procedural History

On January 4, 2016, petitioner timely filed the petition and her exhibits (Pet. Exs.) 1-8. The case was assigned to my docket. ECF No. 4. Petitioner filed a statement of completion on January 6, 2016. ECF No. 6. During an initial status conference on February 10, 2016, I directed respondent to file a status report on whether the case was appropriate for informal resolution, or if respondent wished to proceed on the litigation track, file his report pursuant to Vaccine Rule 4(c) by April 4, 2016. Initial Scheduling Order (ECF No. 8)

On April 4, 2016, respondent filed a report pursuant to Rule 4(c), in which respondent recommended against compensation. Resp. Rep't (ECF No. 9) at 1. Among respondent's objections was that in 2012, the Institute of Medicine ("IOM") concluded that the available evidence did not show an association between inactivated flu vaccine and asthma exacerbation. *Id.* at 5, citing Institute of Medicine, *Adverse Effects of Vaccines: Evidence and Causality* (2012) at 293-296, 345-356, 405-20 [Respondent's (Resp.) Ex. A].

On August 16, 2016, petitioner filed the first expert report and curriculum vitae of Ian Newmark, M.D.[5] Pet. Exs. 11-12. On August 17, 2016, respondent filed a motion for petitioner to file the literature cited in Dr. Newmark's first expert report and a more definite statement from Dr. Newmark, specifically elaborating on his theory of how the vaccine can cause injury lasting

[4] Pursuant to Section 13(a)(1), in order to reach my decision, I have considered the entire record, including all of the medical records, expert testimony, and literature submitted by the parties. This opinion discusses the elements of the record I found most relevant to the outcome.

[5] Dr. Newmark obtained a bachelors' degree in biology in 1975, followed by a medical degree at CUNY Downstate Medical College in New York, New York in 1979. Ex. 12 at 1. Afterwards, he was employed as an intern in internal medicine, chief resident in internal medicine, and then a research fellow in the division of pulmonary disease at Nassau University Medical Center ("Nassau"), which is affiliated with SUNY Stony Brook. *Id.* He served as Associate Director of the Nassau Intensive Care Unit from 1984 to 1987, and Director from 1987 - 1997. *Id.* At the time of the hearing, he was serving as Chief of Pulmonary Disease at Syosset Hospital Northwell Health. *Id.* at 2. In 1984, Dr. Newmark also opened a private practice in which he sees patients primarily with pulmonary disease in both the office and hospital settings. Tr. 41. Dr. Newmark testified that he has "spent most of [his] career, if not all of [his] career, as a clinician taking care of patients". Tr. 43. He estimated that he sees patients with asthma every day, totaling at least 30 patients with asthma every week. *Id.* at 43, 45. Many of the patients have asthma are also classified as obese and/or diagnosed with obstructive sleep apnea. *Id.* at 46. Another significant portion of his patients developed asthma and other respiratory conditions after acting as first responders following the terrorist attack on the World Trade Center on September 11, 2001. *Id.* at 45-47. Dr. Newmark allowed that, because of his focus on clinical practice, he has had "very limited publications." *Id.* at 43. He has taught medical students, residents, and pulmonology fellows throughout his career including at SUNY Stony Brook from 1990 to 2009 and at Hofstra University from 2010 to the present. Ex. 12 at 1-2. Dr. Newmark is licensed to practice medicine in the state of New York and is board-certified in internal medicine (which encompasses pulmonology). *Id.* at 3; Tr. 53. Dr. Newmark has served as an expert witness for both plaintiffs and defendants in medical malpractice cases over the past several decades. *Id.* at 51. This was his first time writing an expert report or testifying in the Vaccine Program. *Id.* at 51-52. Petitioner offered and I admitted Dr. Newmark as an expert in the areas of pulmonology, pulmonary critical care, and internal medicine as it relates to the evaluation, diagnosis, and treatment of asthma-related conditions, asthma exacerbations, and triggers. *Id.* at 52-54.

for more than six months. Resp. Mot. (ECF No. 15). Petitioner did so. Pet. Exs. 13(a) – (k), 14, 15(a) – (d). On December 6, 2016, respondent filed the first expert report, cited literature, and curriculum vitae of Stephen Dreskin, M.D., Ph.D.[6] Resp. Exs. B, B(1) – (14), C.

On February 15, 2017, during a status conference held pursuant to Vaccine Rule 5, I recommended that petitioner should present a modest demand and that respondent consider informal resolution, in view of the limited possible damages and litigative risk on both sides to Scheduling Order (ECF No. 25). Petitioner conveyed a demand, but respondent declined to enter into settlement negotiations. Accordingly, respondent requested that the case be set for an entitlement hearing. Pet. Status Report (ECF No. 26); Resp. Status Report (ECF No. 27).

An entitlement hearing was set for December 4, 2018. Hearing Order (ECF No. 32); Pre-Hearing Order (ECF No. 33). The parties filed simultaneous pre-hearing briefs and a joint pre-hearing submission (ECF Nos. 36, 37, 38). The entitlement hearing took place as scheduled in Philadelphia, Pennsylvania on December 4, 2018. *See* Transcript (Tr.) (ECF No. 44). The witnesses were petitioner, Dr. Newmark, and Dr. Dreskin. *Id.* The parties filed individual post-hearing briefs (ECF Nos. 46, 48, 51). The matter is now ripe for adjudication.

II. Legal Standard

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Human Servs.*, 35 Fed. Cl. 1, 7 (1996) (quoting H.R. No. 908 at 3, *reprinted in* 1986 U.S.C.C.A.N. at 6287, 6344).

A petitioner bears the burden of establishing his or her entitlement to compensation from the Vaccine Program. The burden of proof is by a preponderance of the evidence. § 300aa-13(a)(1). A petitioner may prevail by proving either that (1) the vaccinee suffered an injury listed

[6] Dr. Dreskin obtained a bachelors' degree in biochemistry from the University of Pennsylvania in 1971, a doctorate in physiology from Emory University in 1976, and a medical degree from Emory University in 1977. Ex. C at 1. He then completed an internship and a residency in internal medicine at the University of California – Davis/ Sacramento Medical Center. *Id.* at 2. He then served as a fellow at the National Institute of Allergy and Infectious Diseases at the National Institute of Health ("NIH") from 1981 – 1985. *Id.* He served as a guest researcher and expert on arthritis at the NIH from 1985 – 1988. *Id.* In 1989, Dr. Dreskin joined the University of Colorado ("UC") Medical School where he is now a professor of medicine and clinical immunology, as well as the UC-Denver Medical Center where he is now the medical director of the allergy, asthma, and immunology practice. *Id.*; Tr. 163. Dr. Dreskin estimated that he spends between 75 – 85 % of his time treating patients. Tr. 164. He personally sees approximately five to ten patients with asthma per day. *Id.* at 165-67. Dr. Dreskin spends his remaining professional time on some administrative responsibilities and on conducting research. His publications typically deal with acute allergic reactions and models of food allergy. *Id.* at 164. He runs a lab studying the mechanisms of acute allergic reactions to peanuts specifically. *Id.* His publications do not specifically deal with asthma, but he has published seven articles concerning allergic reactions to vaccines. *Id.*; see also Ex. B at 1; Ex. C at 18-27. Dr. Dreskin is licensed to practice medicine in the state of Colorado and is board-certified in internal medicine, allergy, and immunology. Ex. C at 1. He has provided opinions for the respondent in approximately six prior cases in the Vaccine Program. Tr. 170-71. Respondent offered and I admitted Dr. Dreskin as an expert in the areas of allergy and immunology with a specialized knowledge in asthma. *Id.* at 171.

on the Vaccine Injury Table with onset beginning within a corresponding time period following receipt of a corresponding vaccine (a "Table Injury"), for which causation is presumed or that (2) the vaccinee suffered an injury that was actually caused by a vaccine. Under either method, however, the petitioner must also show that the vaccinee "suffered the residual effects or complications of the illness, disability, injury, or condition for more than six months after the administration of the vaccine." Section 11(c)(1)(D)(i).

Here, petitioner does not allege a Table injury. She bears the burden of establishing causation-in-fact. Petitioner also acknowledges that she had asthma prior to receiving the flu vaccine at issue in this case. Accordingly, her burden is more precisely to establish that she experienced a "significant aggravation" of asthma which was caused in fact by the flu vaccine.

The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). The Federal Circuit first established the legal standard for significant aggravation of a *Table injury. Whitecotton v. Sec'y of Health & Human Servs.*, 81 F.3d 1099 (Fed. Cir. 1996). Then in *Loving*, the United States Court of Federal Claims grafted the first *Whitecotton* prongs onto the three *Althen* prongs, to establish the legal standard for what petitioner needs to establish to prove significant aggravation of an off-Table injury:

> (1) The person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009), citing *Whitecotton*, 81 F.3d 1099; *Althen v. Sec'y of Health & Human Servs.*, 17 F.3d 374 (Fed. Cir. 1994). *See also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (confirming that this is the correct legal standard).

Once a petitioner fulfills the six *Loving* prongs, the burden of persuasion shifts to respondent to show that the alleged injury was caused by a factor unrelated to the vaccination. *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994); § 13(a)(1)(B).

In an early case applying the *Loving* test, then-Chief Special Master Vowell reasoned that the critical point of examination is "whether the change for the worse in his clinical presentation was aggravation or a natural progression of the underlying" condition. *Hennessey v. Sec'y of Health & Human Serv.*, No. 01-190V, 2009 WL 1709053, at *42 (Fed. Cl. Spec. Mstr. May 29, 2009), *motion for review denied*, 91 Fed. Cl. 126 (2010). She noted that it was unclear when this question arises in the analysis and which party has the burden of proof. In *Hennessey*, then-Chief Special Master Vowell found that the petitioner established a post-vaccination significant

aggravation as defined in the Act: "any change for the worse in a preexisting condition which results in markedly greater disability, pain, illness accompanied by substantial deterioration of health." § 300aa-33(4). She then proceeded to evaluate causation-in-fact. She found no logical connection between the vaccination and the significant aggravation of the petitioner's diabetes. Rather, she saw "overwhelming evidence" that the significant aggravation of his diabetes was instead attributable to his pre-existing insulin dependence. *Id.* at *53. She found that the burden never shifted to respondent to demonstrate alternative cause. However, respondent presented "logical and compelling evidence" that an intervening enteroviral infection may have triggered his insulin dependence to cause his post-vaccination change in health. *Id.* at *57-58. She also discussed that the *Loving* test "left open… the nature of petitioner's burden with regard to demonstrating that a vaccine caused an actual change for the worse, versus the natural progression of the underlying injury, disease, or condition." She suggested that the legal standard was "amorphous," but the burden of showing petitioner's condition but-for the vaccination seemed to fall to petitioner. *Id.* at *58-59.

In another case applying the *Loving* test, the special master concluded that the *petitioner* failed to present persuasive evidence that separate[d] [her] problems from an expected course of Crohn's disease". Therefore, she failed to prove significant aggravation. *Locane v. Sec'y of Health & Human Servs.*, No. 99-589V, 2011 WL 3855486 at *10 (Fed. Cl. Spec. Mstr. Feb. 17, 2011), *motion for review denied*, 99 Fed. Cl. 715 (2011), *aff'd*, 685 F.3d 1375 (Fed. Cir. 2012).

The Federal Circuit has confirmed that a special master may consider evidence of other possible causes for the injury, which is relevant to "whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question," *as well* as to a "'factors unrelated' defense on which the government has the burden of proof." *Snyder/ Harris v. Sec'y of Health & Human Servs.*, 553 F. App'x 994, 999-1000 (Fed. Cir. 2014), quoting *Stone v. Sec'y of Health & Human Servs.*, 676 F.3d 1373, 1379-80 (Fed. Cir. 2012).

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Furthermore, a petitioner is not required to present medical literature or epidemiological evidence to establish any *Althen* prong. The special master essentially must weigh and evaluate opposing evidence in deciding whether a petitioner has met her burden of proof. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009); *see also Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992).

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special

masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

An evaluation of an expert's opinion may take into account the factors set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo*, 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). The *Daubert* factors are: "(1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95). However, the Federal Circuit has recently reiterated that the *Daubert* factors are "meant to be helpful, not definitive." *Boatmon v. Sec'y of Health & Human Servs.*, 914 F.3d 1351, 1359 (Fed. Cir. 2019) (citing *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 151 (1999)). In sum, the Federal Circuit "reject[ed] any implication that special masters… must apply *Daubert* in assessing expert testimony, or that each *Daubert* factor must be satisfied." *Id.*

Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280 (holding that Congress created a system in which "close calls regarding causation are resolved in favor of injured claimants"); *Knudsen*, 35 F.3d at 551 ("If the evidence (on alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.").

III. Analysis[7]

A. *Loving* Prong One

This prong requires an "assess[ment] of the person's condition prior to administration of the vaccine[s]." *Loving*, 86 Fed. Cl. at 143.

Petitioner was born in 1959. Tr. 5. She was diagnosed with asthma in 1990, when she was approximately 30 years old. Pet. Ex. 4 at 117. Although there are no medical records from this time, petitioner testified that she was diagnosed with asthma based on one exacerbation which resolved with a one-week course of prednisone. Tr. 9-10. Afterwards, her asthma "was under control, it was dormant" without "any incidents." *Id.* at 9.

Petitioner's primary care provider was Horatio Daub, M.D. at Virtua Family Medicine. His earliest medical record on file is from August 2011. Dr. Daub recorded that petitioner's

[7] Rather than providing a separate summary of the relevant facts before and after the vaccines at issue (drawing from the medical records and the fact witness testimony), I find it appropriate to present that information here, under *Loving* prongs one and two.

body mass index ("BMI") was 50.92, which is classified as obese.[8] Dr. Daub's assessment also included "extrinsic asthma, unspecified" for which he prescribed an albuterol inhaler. He recorded that she was allergic only to penicillin. Pet. Ex. 4 at 140-43.

In December 2011, petitioner complained of "mild intermittent" asthma. She reported using the albuterol inhaler once a week. Pet. Ex. 4 at 134-36. On February 22, 2012, based on a history of "shortness of breath", petitioner underwent a chest x-ray which was normal. Pet. Ex. 4 at 24.[9] In March 2012, she followed up with Dr. Daub, who assessed acute viral bronchitis as well as asthma, for which Dr. Daub prescribed increased use of the albuterol inhaler and a twelve-day course of prednisone. Pet. Ex. 4 at 130-32.

Petitioner was approved for the New Jersey Hospital Care Assistance Program (also referred to as "Charity Care") effective May 31, 2012 for twelve months. This program would cover medical appointments but not prescriptions. Pet. Ex. 7 at 40.[10] She testified that her employment at a company called Stack Transportation ended sometime in 2012. Tr. 12.

In June 2012, Dr. Daub recorded that petitioner's asthma symptoms had worsened and were occurring frequently. She was awakening with cough and dyspnea. She had "cough and wheezing. She also had seasonal rhinitis symptoms. Aggravating factors included "environmental allergens and strong odors/ perfume." Dr. Daub prescribed continued use of the albuterol inhaler and an eight-day course of prednisone. Pet. Ex. 4 at 117-20.

On July 5, 2012, based on a history of "shortness and breath" and "cough", petitioner underwent another chest x-ray. The impression was normal. Pet. Ex. 4 at 19.[11] In August 2012, petitioner followed up with Dr. Daub, who noted her recent presentation to the emergency room. He added to the history: "asthma – moderate persistent exacerbation, 2012, ED eval & nebulizer treatments". Her asthma was "improved but still with mild sx [symptoms]." Dr. Daub prescribed a different inhaler. He also instructed petitioner to avoid (unspecified) "triggers for asthma". Pet. Ex. 4 at 113-16.

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[8] BMI is a measure of body fat based on height and weight that applies to adult men and women. The term "obesity" applies to a BMI of 30 or greater. *See* U.S. Department of Health & Human Services – NIH – National Heart, Lung, and Blood Institute, *Calculate Your Body Mass Index*, at https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm (last accessed March 26, 2020); *see also* Resp. Ex. B at 4.

[9] The February 2012 chest x-ray report was filed among the records possessed by Dr. Daub's office, Virtua Family Medicine. The x-ray report does not indicate where it was performed. No other records from this date have been filed. The physician who ordered the x-ray is currently an emergency medicine doctor affiliated with Virtua Health. *See* Virtua Health – Roy Shubert, M.D., Virtua Family Medicine, https://www.virtua.org/find-a-doctor/physician-detail?id=%7BB6BED4CE-0DF0-434C-AE7E-74ACD705E6E4%7D (last accessed March 24, 2020).

[10] The application for "charity care" is consistent with petitioner's testimony that she was employed at Stack Transportation "from 2010 to 2012" and then worked at Stewart Business Systems "for a year, up until [she] got sick" in the fall of 2013. Tr. at 7-8.

[11] Like the February 2012 chest x-ray report, the July 2012 chest x-ray report was filed within the records from Dr. Daub's office, is not accompanied by any other records, and was ordered by Roy Shubert, M.D.

Dr. Daub referred petitioner to Jewelle Sutherland, M.D. at Virtua Garden State Pulmonary Associates. Pet. Ex. 7 at 46. As part of the initial work up in October 2012, Dr. Sutherland ordered a pulmonary function test. *Id.* at 53. Petitioner blew out 82% of the air in her lungs into the spirometry device within the first second (termed forced expiratory flow or "FEV-1"). After inhaling from a bronchodilator, she demonstrated an increased FEV-1 of 96%. Pet. Ex. 7 at 181-82. Petitioner reported "exercise limitation since February [2012]" and "paroxysms of dry cough particularly when around environmental triggers (her father's dog)". She reported starting a new inhaler, to which she was "intolerant and coughing up… occasional white frothy sputum". Dr. Sutherland recorded that petitioner was allergic to penicillin derivatives and seasonal allergies. Her assessment was "allergic rhinitis", "breathing-related sleep disorder", and "moderate persistent asthma." She added the prescription medication for asthma Advair. Pet. Ex. 7 at 46-49; *see also id.* at 50, 51-52.

In December 2012, petitioner underwent a sleep study. Pet. Ex. 7 at 170-80. The sleep specialist's impression was "severe obstructive sleep apnea".[12] He recommended using a mask and a continuous positive airway pressure ("CPAP") machine[13] every night. He recorded: "Ms. Green is willing to wear CPAP as a nightly treatment." Petitioner's BMI was 54.8. Weight loss would also be beneficial in treating her sleep apnea. *Id.* at 167-69.

In January 2013, petitioner underwent allergy testing. Her general IgE antibody level was 12 IU/ mL (reference range: less than or equal to 158 IU/ mL). Ex. 7 at 28. She had low antibody levels – suggesting no allergies – to oak, several grasses, cat dander, dog dander, Cladosporium, alternaria turius, and house dust mites. *Id.* at 27. This would tend to cast doubt on petitioner's testimony that she had "normal regular allergies" including "hay fever" and "pollens in general", which were controlled with over-the-counter medication. Tr. at 11-12. Petitioner was not tested for allergies to any foods, such as egg. Pet. Ex. 7 at 27. She testified that she was not allergic to any specific foods. Tr. at 12.

Later in January 2013, Dr. Sutherland recorded that petitioner's "sleep was wonderful on the study night after CPAP was applied." She had not obtained the recommended inhaler "for financial reasons." She also reported two days of upper respiratory infection (URI) symptoms. Dr. Sutherland prescribed a cough suppressant and continued use of an inhaler, prescription medication for asthma, and CPAP. Pet. Ex. 7 at 42-44; *see also id.* at 37-39.

There are no further medical records from before the flu vaccine. Petitioner testified that after obtaining the CPAP machine in January 2013, she used it "every night… because [she] coincide[d] that with the asthma. And then [she] just didn't use it as often." She didn't recall

[12] Sleep apnea is defined as "transient periods of cessation of breathing during sleep." *Dorland's* at 117. *Obstructive* sleep apnea "result[s] from collapse or obstruction of the airway with the inhibition of muscle tone that occurs during REM sleep. In adults it is seen primarily in middle-aged obese individuals." *Id.*

[13] CPAP machines are one type of: "Positive airway pressure machines, used with a variety of breathing masks, [which] are the most widely used treatment for moderate and severe sleep apnea." American Sleep Apnea Association, *Positive Airway Pressure Devices*, https://www.sleepapnea.org/treat/sleep-apnea-treatment-options/ (last accessed March 24, 2020).

when she stopped using it as often. Petitioner was using the CPAP machine "sporadically", if at all, by the time of the vaccination in September 2014. Tr. 36-38.

Petitioner testified that she "didn't keep going to the doctor because she was okay." Tr. 17. However, she did not have an accurate memory of the 2012 asthma exacerbation – including thinking that it occurred in the fall (when the medical records support that it began in February), that it resolved after one course of steroids (actually two), and that it resolved within a week (while it actually went on for months). Tr. 10-17.

Petitioner also testified that after January 2013, there was no further medical attention because she "didn't have insurance." Tr. 17. However, the contemporaneous records support that petitioner was enrolled in charity care beginning in May 2012 and subsequently had several appointments with her primary care provider, the pulmonologist, and sleep specialist over the subsequent months. It is not clear what changed in January 2013. Additionally, she testified that she became employed again and gained health insurance in fall 2013, which would also reduce the barriers to medical treatment. *See* Ex. 2 at 4 (September 2014 medical record reflecting that she had Aetna health insurance). All in all, petitioner appeared to be an honest but imperfect historian. Due to the lack of contemporaneous medical records, her medical condition from the end of January 2013 to September 22, 2014 is not particularly clear.

B. *Loving* Prong Two

This prong requires an assessment of "the person's current condition (or the condition following the vaccination[s] if that is also pertinent)." *Loving*, 86 Fed. Cl. at 143.

On Monday, September 15, 2014[14], petitioner received an inactivated trivalent standard dose influenza vaccine (brand name: Fluvirin). Pet. Ex. 1.[15] Petitioner testified that she received the vaccine because of her job at Stewart Business Systems, a company that provided computer equipment to medical institutions. Tr. at 7-8. She testified that this was the first flu vaccine she had ever received. *Id.*

Petitioner testified that approximately five days after vaccination, on Saturday, September 20, 2014, she developed "a sensitivity to scents, to smells, severe coughing, shortness of breath, and her chest getting tight." Tr. 16-17.

Seven days after the vaccination, on Monday, September 22, 2014, in the morning, petitioner walked into her workplace and "couldn't catch her breath." Tr. 21. Then she started coughing with foam. Petitioner also testified: "Right when I had the episode in 2014, I remember the people coming in cleaning the bathroom with bleach, that set it off." *Id.* at 32. She knew from prior experience that she was having an asthma exacerbation. Tr. at 21. But she

[14] *See* September 2014 Calendar, available at https://www.calendar-365.com/calendar/2014/September.html (last accessed March 24, 2020).

[15] *See Influenza Virus Vaccine Inactivated*, https://www.drugs.com/monograph/influenza-virus-vaccine-inactivated html [Ex. 13(k)].

also characterized this event as "fast and hard and with a vengeance… it was worse than 2012, the intensity of it." *Id.* at 19. She had medical insurance by that time. *Id.* She could have gone to her primary care provider Dr. Daub or to her pulmonologist Dr. Sutherland. *Id.* at 19-20. Instead, because the attack was so severe, she drove herself to the emergency room. *Id.* at 20-21. At 8:30 a.m., petitioner presented to the emergency room at Virtua Memorial Hospital in Mount Holly, New Jersey. Pet. Ex. 2 at 5. She was noted to have Aetna health insurance. *Id.* Her chief complaint was "asthma SOB [shortness of breath]." *Id.* Upon evaluation, petitioner reported that the onset of symptoms was "gradual" and "onset was 2 days prior to arrival." *Id.* at 9. She described that this episode was "similar" to her "previous episodes." *Id.* After receiving two nebulizer treatments and prednisone, petitioner improved. *Id.* She was discharged at approximately 11:30 a.m. with instructions to use her inhaler, take prednisone, and follow up with her primary care provider. *Id.* at 7. Her BMI was recorded to be 60.07. *Id.* at 10.[16]

On Wednesday, September 24, 2014, petitioner returned to the Virtua Memorial Hospital emergency department for further asthma symptoms. Pet. Ex. 2 at 23-33. Of note to respondent's expert Dr. Dreskin, lab work revealed an eosinophil absolute count of 0.03 x 10(3)/mcL (compared to a reference range of 0.00 – 0.70 x 10(3)/mcL). *Id.* at 31. Upon admission, she was evaluated by Erik DeLue, M.D. He recorded that petitioner developed shortness of breath "last week" and started coughing on "Friday" (which would have been on September 19, 2014). Ex. 3 at 13. A coworker had been sick, but petitioner did not believe that she had cold-like symptoms. *Id.* "She presented to the emergency room on Monday when she was started on steroids. This did not seem to help significantly so she presents again today…" *Id.* Dr. DeLue's assessment was "asthma exacerbation". *Id.* He recommended continuing nebulizer treatment and steroids. *Id.* Additionally: "Given her asthma seems to be worsening in the past year [he would] consult pulmonary for further recommendations and probably outpatient follow up." *Id.* On September 30, 2014, petitioner was discharged with prednisone, an inhaler to use twice a day, and albuterol for a nebulizer to take as needed. Pet. Ex. 3 at 15-18.[17]

On October 2, 2014, petitioner followed up with Dr. Daub regarding her asthma exacerbation. Under history of present illness ("HPI"), he recorded "The symptoms began on 09/21/2014 and generally lasts for 12 days… Aggravating factors include started 4 days after got flu shot [which would be 09/19/2014]." Dr. Daub's assessment was "asthma exacerbation". His impression was "see HPI". He continued prednisone and albuterol. Pet. Ex. 4 at 108-10.[18]

[16] Petitioner testified that at the hospital, a doctor asked her questions including whether she had recently been outside of the United States (no), whether she had been around anyone seriously ill or coughing (no), and whether anything out of the ordinary had occurred recently (that she had received a flu vaccine). Tr. 22.

[17] Petitioner disagreed with Dr. DeLue's assessment that her asthma "seem[ed] to be worsening in the past year". She testified that her asthma only worsened after she received the flu vaccine on September 15, 2014. Tr. 35.

[18] Petitioner testified that Dr. Daub asked about the circumstances around the September 2014 asthma exacerbation. He asked whether she had been out of the country (no) or whether she had been around anyone sick (no). She reported that she had received a flu vaccine and that Dr. Daub told her not to get any further flu vaccines. Tr. 25-26.

On October 3, 2014, petitioner began receiving physical therapy to regain her endurance, strength, and balance following her hospitalization for asthma exacerbation. Pet. Ex. 3 at 8. On October 16, 2014, Dr. Daub recorded about petitioner's asthma: "Onset: on 09/22/2014. The initial visit date was 06/25/2012. Symptoms began in 1990… Context: exercise-induced and systemic steroid use (intermittent). Aggravating factors include exercise and respiratory infection. Symptom relief is noted with beta-agonist/ anticholinergic inhaler, oral steroid use, rest, and flu shot." Petitioner's asthma was "gradually improving" but she was still coughing ("wheezing") without prednisone. He referred her to a pulmonologist. Pe. Ex. 4 at 103-07.

On October 20, 2014, petitioner returned to the emergency room. She endorsed shortness of breath, coughing, and yellow sputum as well as fever, chills, and one episode of vomiting (emesis), intermittent nausea, and decreased appetite. Pet. Ex. 2 at 40-41. She was discharged later that evening with an assessment of asthma and upper respiratory infection. Ex. 2 at 43. She was prescribed a cough suppressant and prednisone. *Id.* at 51.

On October 30, 2014, Dr. Daub recorded that petitioner's asthma "symptoms began on 09/15/2014" and "the aggravating factors include initially flu shot then recently had cold". She was still having significant dyspnea and wheezing with even mild exertion doing activities of daily living. Dr. Daub added home occupational therapy. Pet. Ex. 7 at 107-110.

At the next visit on November 13, 2014, Dr. Daub recorded that the asthma symptoms "began on 09/22/2014… shortly after getting flu shot". The aggravating factors were "flu shot" as well as "any sprays or perfumes". Petitioner had three exacerbations in the past ten days and was using her nebulizer regularly, every two to four hours. Dr. Daub reiterated that petitioner should see a pulmonologist. Pet. Ex. 4 at 99-100.

On November 26, 2014, Emilio Mazza, Jr., M.D., Ph.D., at Garden State Pulmonology Associates saw petitioner for an initial consult.[19] Under history of present illness, he recorded: "She states that she was doing well with her asthma until September 15 when she had an allergic reaction to the flu shot." Dr. Mazza's assessment was an asthma exacerbation which "likely relate[d] to her recent allergic reaction to the influenza vaccine." Dr. Mazza planned a pulmonary function test. He also noted that petitioner had "very severe obstructive sleep apnea", but she hadn't used her CPAP machine "for about a year." He explained that "there are significant cardiovascular morbidities associated with untreated severe obstructive sleep apnea" and she should resume use of the CPAP machine. Dr. Mazza also noted that petitioner had gained weight (since seeing his colleague Dr. Sutherland two years prior) and that petitioner should lose weight. Pet. Ex. 7 at 101-03.[20]

[19] Dr. Mazza at recorded under history of present illness: "Follow Up of Asthma. The initial visit date was June 25, 2012." Upon review, it appears that on June 25, 2012, petitioner was seen by her primary care provider Dr. Daub, who referred her to Dr. Sutherland at Garden State Pulmonology Associates. *See* Ex. 4 at 4 at 117-20; Ex. 7 at 46-49. Petitioner's initial consult with Dr. Mazza, who was also affiliated with Garden State Pulmonology Associates, was in fact on November 26, 2014. Ex. 7 at 101-06.

[20] Petitioner testified that Dr. Mazza told her not to receive further flu vaccines. Tr. at 28-33. That recommendation does not appear in his records.

In December 2014, petitioner was discharged from physical therapy and occupational therapy. Pet. Ex. 3 at 8. Dr. Daub recorded improvement with prednisone and resumed use of the CPAP machine. Petitioner was experiencing chest pains, for which she was referred to a cardiologist. Pet. Ex. 4 at 84-88. The cardiologist, Thomas Galski, D.O., felt that petitioner had "some degree of volume overload plus or minus right-sided heart failure/ pulmonary hypertension concomitant with her sleep apnea, asthma, and obesity." Dr. Galski also ordered an echocardiogram which found a left ventricle ejection fraction of 70 – 75%. Pet. Ex. 5 at 16-24.

In January 2015, petitioner went to the emergency room for dyspnea and chest tightness. Of note to respondent's expert Dr. Dreskin, lab work revealed an eosinophil count of 0.27 x 10(3)/mcL (compared to a reference range of 0.00 – 0.70 x 10(3)/mcL)). Pet. Ex. 2 at 95-125.

On follow up with Dr. Galski, petitioner "admit[ted] that she [did] not use her CPAP mask consistently and actually has now admitted that she has not worn it since prior to follow wean [sic; meaning unclear?]. She does have occasional nocturnal choking spells and dyspnea." Ex. 5 at 10. Dr. Galski's impression was that petitioner's asthma, non-compliance with CPAP therapy, and obesity were all contributing to her dyspnea. Pet. Ex. 5 at 10-14.

Beginning in approximately February 2015, Dr. Daub's records provide that petitioner was allergic to flu vaccine. Pet. Ex. 4 at 80-82.

In March 2015, Dr. Mazza recorded that petitioner was "wearing her CPAP every night. She love[d] her CPAP." However, she was having "the second exacerbation in about a month". She was administered albuterol via a nebulizer in the office. Pet. Ex. 4 at 75-79. Dr. Mazza also conducted a pulmonary function test. Petitioner's FEV-1 was 66%. She could not repeat the test after bronchodilation "due to coughing and vomiting". Pet. Ex. 7 at 166.

Dr. Mazza recommended a total IgE antibody level and an allergy panel. Pet. Ex. 7 at 230-35; Pet. Ex. 10 at 7-11. In July 2016, Dr. Daub recorded that petitioner had "increased allergy symptoms in Spring, Summer, & Fall. Never got allergy tests order [sic] by Dr. Mazza." Dr. Daub assessed petitioner with allergic rhinitis, then re-ordered the allergy testing and other lab work. The resulting general IgE antibody level was 17 IU/ mL (reference range: 0 - 100 IU/ mL). She had insignificant antibody levels to all of the allergens tested. Pet. Ex. 3-7, 13, 18-19.

In February 2017, Dr. Mazza recorded that petitioner had been coughing more and using her nebulizer more frequently over the past few days. Dr. Mazza was worried that she was at the start of another asthma exacerbation. Pet. Ex. 19 at 9-15. He conducted a repeat pulmonary function test. She demonstrated a FEV-1 score of 92% before and 93% after bronchodilation. She could not complete another aspect of the test: diffusing capacity because of persistent coughing. Her test was interpreted as "normal" with "mild restrictive impairment". *Id.* at 22-25.

In April 2017, Dr. Daub recorded that petitioner's asthma exacerbation in early February had resolved. Pet. Ex. 18 at 8-12. In September 2017, Dr. Mazza recorded that she had another exacerbation necessitating another nebulizer treatment in the office. This "seem[ed] to have been triggered by exposure to a child with a URI." Pet. Ex. 19 at 16-21. The last medical records on file are from December 2017, when petitioner returned to the urgent care facility

reporting a five-day history of productive cough and chest congestion. The assessment was asthma exacerbation associated with acute bronchitis. Pet. Ex. 17 at 11-14, 22-25.

At the entitlement hearing, petitioner testified that she has continued to have asthma exacerbations which are set off by various scents, changes in temperature, and other things. She had an asthma attack "just from stress" the morning of the entitlement hearing. Tr. at 31-32.

C. *Loving* Prong Three

Under *Althen* prong three, petitioner has the burden of establishing that she suffered a significant aggravation of asthma following the flu vaccine on September 15, 2014. Significant aggravation is defined as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). In this case, the medical records supplemented by the testimony reflect that following the September 15, 2014 flu vaccine, petitioner has indeed suffered a significant aggravation of her asthma. However, this does not constitute a finding that the significant aggravation was caused by her flu vaccine. That issue will be addressed below.

D. *Loving* Prong Four (*Althen* Prong One)

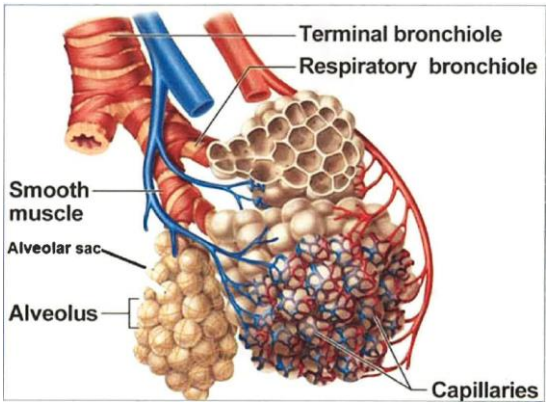
Under *Althen* prong one, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). It must only be "legally probable, not medically or scientifically certain." *Id.* at 549. The Federal Circuit explained in *Althen* that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen*, 418 F.3d at 1280 (emphasis added).

1. Introduction to Asthma

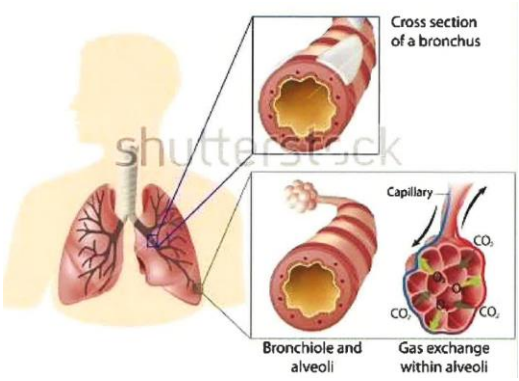
Asthma is defined as "recurrent attacks of paroxysmal ["sudden" and "intens[e]"] dyspnea ["breathlessness or shortness of breath; difficult or labored respiration"], with airway inflammation and wheezing due to spasmodic contraction of the bronchi." *Dorland's* at 168, 582, 1384. The bronchi are "the larger air passages of the lungs". *Id.* at 251, 254. Some cases of asthma are allergic manifestations in sensitized persons [described as *allergic* or *atopic*); others are provoked by factors such as vigorous exercise, irritant particles, psychologic stresses, and others." *Dorland's* at 168. *Extrinsic* asthma is: "caused by some factor in the environment, usually atopic asthma. Onset is usually in childhood and almost always before age 30." *Id.* In contrast, *intrinsic* (also called *cryptogenic*) asthma is "attributed to pathophysiologic disturbances and not to environmental factors; usually seen in adults." *Id.*

At the start of the entitlement hearing, I showed a number of images to both parties' counsel and experts. The experts agreed on two images that would be the most helpful in understanding the lung anatomy as it is relevant to asthma. These two images were introduced as Court's Exhibits 1-2, which are provided below.

Court's Exhibit 1



Court's Exhibit 2



In discussing the above two images, Dr. Newmark explained that the airways are not fixed tubes. Tr. 58. There is smooth muscle on the exterior and an inner lining. *Id.*

During an acute asthma exacerbation (also called an attack), the smooth muscle constricts. *Id.* The lining can swell and develop edema which can block the airways. *Id.* The lining can also produce mucus which can "plug" the smaller bronchi, referred to as bronchioles, which can prevent air from entering the alveoli where gas exchange occurs, blood is oxygenated, and carbon dioxide is expended. *Id.* at 58-59. If mucus plugs the distal bronchioles, air cannot be exchanged. *Id.* at 59. Dr. Dreskin agreed with this explanation. Tr. 173-74.

The experts agreed that the hallmark symptoms of an asthma attack are shortness of breath, wheezing, coughing, and possibly sputum production. Tr. 59, 62-63, 174. Dr. Newmark added that if a respiratory infection is the cause, the person may also have symptoms such as fever, chills, green or yellow sputum. *Id.* at 63.

The treatments for asthma include bronchodilators such as albuterol (which have various delivery methods including rescue inhalers and nebulizer machines). Bronchodilators can reverse at least the inflammation and smooth muscle constriction. Tr. 100, 172-73. The bronchodilators can be enhanced by steroids such as prednisone. *Id.* at 100. These steroids can also reduce inflammation of the mucosa, reduce mucus production, and cause less swelling. *Id.*

Dr. Newmark opined that an asthma exacerbation can also cause residual effects lasting for more than six months and even permanently. He opined that asthma exacerbation involves smooth muscle constriction, mucus secretion, and airway wall edema; sometimes these features persist, even in patients that receive aggressive therapy. The acute asthma exacerbation can also be followed by persistent increased reactivity to all matter of stimuli (not limited to what caused the initial event) as well as decreased PEV-1. Pet. Ex. 14 at 1-3, citing Brooks et al., *Reactive Airways Dysfunction Syndrome (RADS): Persistent Asthma Syndrome After High Level Irritant Exposures,* 88 Chest 376 (1985) [Ex. 15(b)]; Folkerts et al., *Virus-Induced Airway Hyperresponsiveness and Asthma,* 157 Am. J. Resp. Crit. Care Medicine 1708 (1998) [Pet. Ex. 15(a)]; Fish et al., *Airway Remodeling and Persistent Airway Obstruction in Asthma,* 104 J. Allergy Clin. Immunol. 509 (1999) [Pet. Ex. 15(c)]; *see also* Fish et al., *The Safety of Inactivated Influenza Vaccine in Adults and Children with Asthma,* 345 N. Engl. J. Med. 1529 (2001) [Pet. Ex. 15(d)]. Dr. Newmark opined that every individual responds differently and that an acute asthma exacerbation can cause some or all of these changes, to result in a permanent worsening of that individual's baseline asthma status. Tr. 62, 97-99.

Respondent's expert Dr. Dreskin agreed that an asthma exacerbation increases the likelihood of future exacerbations, even those separated in time. He opined that exacerbations tends to get worse. That is the natural history of asthma. Tr. 177, 186, 200-01, 235-36.

Upon review, the experts agree that one asthma exacerbation can cause further asthma exacerbations. Accordingly, I find that one asthma exacerbation can cause the significant aggravation of asthma. Accordingly, the remaining disputes in this case are whether a flu vaccine can cause an asthma exacerbation, whether the flu vaccine did cause petitioner's asthma exacerbation in September 2014, and whether there is an acceptable temporal association.

2. Petitioner's Expert's Opinion Regarding *Loving* Prong Four (*Althen* Prong One)

Dr. Newmark has given "many thousands of influenza vaccines personally and in [his] office". Tr. 105. He recommends flu vaccine to his patients with asthma, as they are at high risk for complications if they contract the live flu virus. *Id.* Thus, he said it is "absolutely recommended" that people with lung disease receive flu vaccines every year. *Id.*

However, Dr. Newmark opined that flu vaccines can cause asthma exacerbations in some individuals. In his reports, he opined that flu vaccines have components including viral protein and egg protein to which some individuals are allergic. Pet. Ex. 11 at 3-4. At the hearing, Dr. Newmark confirmed that his theory was specifically about egg protein. Tr. 77, 116-17.

Dr. Newmark opined that in an individual with asthma and egg allergy, flu vaccine can cause an allergic response, which he termed an "IgE-mediated sensitization" resulting in asthma exacerbation. Pet. Ex. 11 at 3-5; Tr. 77, 116-17. He quoted from a webpage which provides that inactivated flu vaccine has been associated with rare reports of "immediate, presumably allergic reactions (e.g., urticaria, angioedema, anaphylaxis, anaphylactic shock, serum sickness, and allergic asthma." Ex. 11 at 3, citing *Influenza Virus Vaccine Inactivated*, https://www.drugs.com/monograph/influenza-virus-vaccine-inactivated.html [Pet. Ex. 13(k)].

Dr. Newmark filed a 1997 review article which provides: "Egg allergy is a contraindication to influenza immunization because of the traces of egg antigen contained in inactivated vaccines following their production in hens' eggs." Watson et al., *Does Influenza Immunisation Cause Exacerbations of Chronic Flow Obstruction or Asthma?*, 52 Thorax 190 (1997) [Pet. Ex. 13(d)] at 2. Watson et al. also stated: "Little information is therefore available about the effect of vaccination in asthmatics with egg allergy, but one small uncontrolled trial was reported by Murphy and Strunk, who administered an inactivated influenza vaccine to six asthmatic children with egg allergy using a low dose incremental scheme; no subsequent respiratory symptoms were reported." Pet. Ex. 13(d) at 2-3. Dr. Newmark did not file any studies evaluating flu vaccine and asthma exacerbation in individuals with known egg allergies. Many of the studies cited by Dr. Newmark, discussed further below, excluded subjects with known egg allergies. *See* Anand et al., Pet. Ex. 13(a); Nicholson et al., Pet. Ex. 13(c); Kmiecik et al., Pet. Ex. 13(e); Ouellette et al., Pet. Ex. 13(h); Cates et al., Pet. Ex. 13(f).

Dr. Newmark opined that two studies showed "increased bronchial reactivity to bronchoprovocation test in individuals with asthma for several days after vaccination against influenza." Pet. Ex. 11 at 4, citing Ouellette et al., *Increased Response of Asthmatic Subjects to Methacholine after Influenza Vaccine*, 36 J. Allergy 559 (1965) [Pet. Ex. 13(h)]; Anand et al., *Effect of Influenza Vaccine on Methacholine (Mecholyl) Sensitivity in Patients with Asthma of Known and Unknown Origin*, 42 J. Allergy 187 (1965) [Pet. Ex. 13(a)]. These studies did report increased bronchial reactivity in the vaccinated subjects with asthma, compared to the vaccinated subjects without asthma, but only in the first 72 hours. Additionally, the studies were designed to replicate certain effects of respiratory infection while avoiding local bronchial inflammation. They were not designed to evaluate the safety of flu vaccines. On cross-examination, Dr. Newmark agreed that the flu vaccines used in those studies were very different than what is used today. For example, the older flu vaccines caused fever at a much higher rate. Tr. 117-18. Dr. Newmark also acknowledged that later studies generally did not observe the same changes in pulmonary function. *Id.* at 118-20, 141-42 (discussing Watson et al., Pet. Ex. 13(d) at 2).

Dr. Newmark also cited Nicholson et al., *Randomised Placebo-Controlled Crossover Trial on Effect of Inactivated Influenza Vaccine on Pulmonary Function in Asthma*, 351 Lancet 326 (1998) [Pet. Ex. 13(c)]). The study participants were adults with preexisting asthma and no known egg allergies. Their health status was reviewed two weeks before the first injection of either flu vaccine or placebo; at their first injection visit; two weeks later, when they received the second injection; and two weeks thereafter. Pet. Ex. 13(c) at 2. The primary clinical outcome measure was "an asthma exacerbation occurring within 72h of injection, defined as a decline in early-morning PEF [peak expiratory flow] of more than 20% compared with the lowest of the best three early-morning PEF values during the 3 days before the vaccination." *Id.* at 3. The

secondary measures were changes in mean PEF values, colds coinciding with exacerbations, increased use of medication (including beta blockers, antibiotics, and steroids), unscheduled medical consultations, and hospital admissions for asthma exacerbations. *Id.*

Nicholson et al. found that between the participants receiving placebo and the participants receiving repeat flu vaccine, there was no significant difference in decreased PEF of more than 20%. *Id.* at 6. Participants receiving flu vaccine *for the first time* did have significantly more decreases in PEF of more than 20%. *Id.* at 6. However, within that group of first-time flu vaccinees, when participants with colds were excluded, "the association between vaccine and decreases in PEF was no longer significant for any decrease of more than 20%". *Id.*

Dr. Newmark opined that Nicholson et al. showed that first-time vaccinees have a higher incidence of adverse events. Tr. 101-04, 132-37. Nicholson et al. do posit: "either an asthmatic patient's initial exposure to influenza vaccine is more likely than subsequent doses to affect pulmonary function adversely, or that patients who initially suffer an adverse pulmonary event after vaccination, who may be more likely to do so again, avoid further doses." Pet. Ex. 13(c) at 8. However, Nicholson et al. only found that first-time vaccinees had a non-significant increase in decreased PEF values of more than 20%, for a few days after being vaccinated. Additionally, Nicholson et al. did not detect any significant differences between placebo and flu vaccine in regard to respiratory symptoms, increased use of medication, unscheduled medical consultations, and hospital admissions for asthma exacerbations. *Id.* at 6-8.

Dr. Newmark also filed Christy et al., *Effectiveness of Influenza Vaccine for the Prevention of Asthma Exacerbations*, 89 Arch. Dis. Childhood 734 (2004) [Pet. Ex. 13(g)]. This was a retrospective study of 800 children, half of whom received flu vaccine and half of whom did not. *Id.* at 1. Christy et al. found that the children receiving flu vaccine had a higher number of clinic visits, emergency department (ED) visits, and hospitalizations for asthma in the subsequent year. *Id.* Christy et al. discussed that these findings were "surprising" but: "One must consider the main limitation of this retrospective study: the possibility that vaccination was somehow merely a marker for bad asthma." *Id.* They asked whether "only children with severe asthma received the vaccine, then the vaccine group might do worse for that reason." *Id.* They also "considered whether high health care utilization may 'cause' vaccination, rather than vice versa because children who go to the doctor more often are more likely to receive vaccination." *Id.* Accordingly, Christy et al. recommended "a long-term, prospective trial" on this issue. *Id.* at 2. *See also* Kmiecik et al., *Influenza Vaccination in Adults with Asthma: Safety of an Inactivated Trivalent Influenza Vaccine*, 44 J. Asthma 817 (2007) [Pet. Ex. 13(e)] at 5-6 (stating that the Christy et al. study was limited by a lack of detail about the severity of the subjects' asthma, the lack of a control group, and no way to conclude whether severe asthma prompted vaccination).

Dr. Newmark also filed Kmiecik et al.'s study of 286 adults with atopic (allergic) asthma. Approximately half of the subjects (144/286) received either flu vaccine followed by placebo 14 days later ("Group A"). The other half (142/286) received placebo followed by flu vaccine 14 days later ("Group B"). Dr. Newmark emphasized that group A had higher incidences of asthma exacerbations over the subsequent 14 days. Pet. Ex. 11 at 4-5; Tr. 107-08. In contrast, the authors emphasized: "When considering Groups A [flu vaccine before placebo] and B [vaccine before placebo] separately, significantly more exacerbations occurred in each group during the

first 14-day study period than during the second 14-day period… While we could not determine why more exacerbations occurred during the first study period before crossover, this result indicates that the sequence of vaccination was not likely to have affected the occurrence of an asthma exacerbation." Pet. Ex. 13(e) at 5. In their conclusion, Kmiecik et al. support that individuals with atopic asthma should receive flu vaccines, which is unlikely to be associated with exacerbations. *Id.* at 6.

Dr. Newmark also filed Fleming et al., *Comparison of the Efficacy and Safety of Live Attenuated Cold-Adapted Influenza Vaccine, Trivalent, with Trivalent Inactivated Influenza Virus Vaccine in Children and Adolescents with Asthma*, 25 Pediatr. Infect. Dis. J. 860 (2006) [Pet. Ex. 13(j)]. This study was designed to compare the efficacy of different methods of administration of flu vaccine in children with asthma. *Id.* at 2. Compared to the asthmatic children receiving intramuscular vaccines, the asthmatic children receiving intranasal vaccines had significantly more reports of runny nose and rhinitis in the measured 14-day period. Between the groups, there were no significant differences in rates of asthma exacerbation, mean PEFR, asthma symptom scores, or nighttime awakening scores. *Id.* at 9. Of note, this study did not include controls, such as children who received placebo via intranasal and/or intramuscular vaccination, or children who received nothing at all.

Finally, Dr. Newmark filed Cates et al., *Vaccines for Preventing Influenza in People with Asthma (Review)*, 2 Cochrane Database of Systematic Reviews, doi: 10.1002/14651858.CD000364.pub4 (2013) [Pet. Ex. 13(f)]. This is a review of "the best available evidence regarding the effectiveness of influenza vaccination in patients with stable asthma." Pet. Ex. 13(f) at 17. Cates et al. acknowledged Nicholson et al.'s paper finding decreased PEV flow following first-time vaccination. However, Cates et al. summarized that the likelihood of an asthma exacerbation following influenza vaccination is low and "the absolute difference in risk of exacerbation between active vaccination and placebo lies between a 4% reduction and 5% increase, respectively." *Id.* They recommended further randomized controlled trials on flu vaccine and asthma exacerbations. *Id.*

Dr. Newmark testified: "There's not been a complete study looking at severe chronic exacerbation in asthma due to influenza vaccine" but the above studies indicate that there *is* a risk. Tr. 105-06. Dr. Newmark opined that the consensus is that flu vaccines are "generally safe, but there are individuals that are going to have risk." *Id.* at 105. He opined that the risk "may be anywhere between 3 percent and over 20 percent in terms of having an exacerbation from the influenza vaccine, depending on the study you look at." *Id.*

In his reports (Pet. Exs. 11, 14), Dr. Newmark did not address the IOM's 2012 publication evaluating the evidence and causality regarding adverse events of vaccines, which concluded: "The evidence favors rejection of a causal relationship between inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes in children and adults." Resp. Ex. A at 17. At the hearing, Dr. Newmark opined that the IOM cited studies, including many cited in his reports, that showed a temporal association between flu vaccine and asthma exacerbations. He allowed that temporal association in and of itself does not prove causation. He opined that in clinical practice, temporal association between a potential stimulus and an asthma exacerbation in the absence of any other explanation would support causation. He

disagreed with the IOM's conclusion that the evidence did not support a causal relationship. Dr. Newmark allowed that he did not have any expertise in epidemiology, but he did have considerable clinical experience with asthma patients. Tr. 124-29.

Finally, during the entitlement hearing, Dr. Newmark and I had a colloquy about how a primary IgE-mediated allergic reaction may be followed by a secondary cytokine-mediated response. Tr. 82-84. On cross-examination, respondent's counsel asked whether Dr. Newmark had suggested "that the IgE response then results in an adverse reaction to secondary cytokines anywhere on the record before today, correct?" Tr. 154. Dr. Newmark answered: "That's correct." *Id.* Dr. Newmark did not sufficiently develop this theory before the hearing, and he did not offer any supporting literature. Thus, this theory will not be accorded significant weight.

3. Respondent's Expert's Opinion Regarding *Loving* Prong Four (*Althen* Prong One)

Dr. Dreskin opined that the available evidence did not support a finding that flu vaccine can cause asthma exacerbation.[21] He opined that the Anand and Ouellette studies were published several decades ago, when the pharmacologic treatment was far less good than today and the vaccine formulations were different (e.g., less pure). Resp. Ex. B at 6-7. Nicholson et al.'s finding of decreased PEV-1 following flu vaccine was not significant, when colds were excluded. Resp. Ex. B at 7. "All these caveats aside, even in the patients with increased sensitivity to inhaled methacholine, in the Anand and Ouellette studies, the enhanced sensitivity was back to baseline in 48-72 hours. The Nicholson study looked at outcomes within 72 hours." Resp. Ex. B at 7. At the hearing, Dr. Dreskin added that these studies showed decreased PEV-1 but not corresponding clinical effects. Tr. 209-10.

Dr. Dreskin also opined that the Anand, Ouellette, Nicholson, Hassan, and Daggett publications were all about asthma exacerbations occurring within the first one, two, or three days after vaccination. Dr. Dreskin opined that these studies were not relevant to the current case, in which petitioner had the onset of worsened asthma symptoms five days after vaccination (which is discussed further below). Resp. Ex. B at 7.

He emphasized that Christy et al. suggested an association between flu vaccine and increased healthcare utilization for asthma exacerbation based on only a retrospective study. Additionally, the authors wrote that the main limitation of their study was the possibility that vaccination was simply a marker for bad asthma. Resp. Ex. B at 7; *see also* Tr. 216-18.

Dr. Dreskin opined that Cates et al.'s review of the available literature noted certain findings by Nicholson et al. and Christy et al., but nevertheless concluded that flu vaccine was not associated with asthma exacerbations. Resp. Ex. B at 7; *see also* Tr. 211-14.

[21] Dr. Dreskin also challenged petitioner's expert's opinion about the medically acceptable temporal association between an allergic stimulus and asthma exacerbation. Ex. B at 5. This will be addressed below, under *Loving* prong six (*Althen* prong three).

Dr. Dreskin opined that the IOM, in its 2012 publication, was more rigorous but came to the same conclusion: that the evidence favored rejection of a causal relationship between inactivated flu vaccines and asthma exacerbation. Tr. 213, referencing Resp. Ex. A. I stated that there is general agreement that vaccines are beneficial for preventing infection with the live virus. Tr. 214. The Vaccine Program is not tasked with evaluating vaccine safety overall, but with evaluating possible vaccine causation for rare events in the individual cases filed. *Id.* I asked whether the IOM's conclusion "eliminate[s] the likelihood of the rare events" or whether "some of these other papers that pick up some differences are more helpful in understanding whether something could be occurring?" *Id.* Dr. Dreskin responded that rare events do occur, but "the issue at hand has to do with causality". *Id.* at 214-15. He opined that "these rare events of asthma exacerbations happen after placebo… and they happen after vaccine." *Id.* at 215. I stated that some of the articles seem to show that the incidence is higher after flu vaccine. *Id.* Dr. Dreskin responded: "Yes. Some of them somewhat… But that speaks – there's not enough there there to get to causality. There may be a little bit of there there, but there's not much there there, if I can say that without being confusing." *Id.* On cross-examination, Dr. Dreskin opined that he did not require epidemiology to prove causation. *Id.* at 231.

Dr. Dreskin emphasized that biological plausibility is also important. Tr. 219. On cross-examination, petitioner's counsel asked about the meaning of "biologically plausible". *Id.* at 227. Dr. Dreskin opined that "given our current knowledge of biology, that you can connect the dots from A to B to C." *Id.* "So given A, given B… the dot between A and B makes mechanistic sense." *Id.* Petitioner's counsel asked what kind of evidence is required. *Id.* at 227-28. Dr. Dreskin responded that the evidence can be varied. *Id.* at 228. "They could be studies in humans, studies in animals, understanding of how molecule A may interact with a cell B to cause an event C where things have been shown experimentally to be true, or in the context of a variety of experiments, that they simply make sense in terms of what we understand about biology." *Id.* Dr. Dreskin opined that case studies are useful for generating hypotheses, but then those hypotheses need to be tested. *Id.*

I asked Dr. Dreskin about his clinical experience. Tr. 218. He agreed that often, he does not have a study in hand that justifies the decision he makes in treating a patient. Tr. 218-19. He stated: "We study populations. We treat individuals." *Id.* at 219. He also opined that clinical experience can be considered, but it has to be questioned. Tr. 228. He has had experiences in which initially, the patient's assertion that he or she had an allergic reaction to a particular stimulus "makes sense", but he conducts an evaluation (including lab work and observed introduction of the stimulus) which rules out the suspected allergy. *Id.* at 228-34.

I also asked, if a person with mild asthma contracted the live influenza virus, whether that would potentially cause asthma exacerbation. Tr. 193-94. Dr. Dreskin answered yes, because a person with mild asthma has a highly reactive airway. *Id.* at 194. A live virus such as influenza can enter the respiratory epithelium, where it can activate cytokines and inflammation, resulting in constriction of the airway. *Id.* Dr. Dreskin opined that the virus has cytotoxic effects on the cells and that the immune response to the virus also contributes in a "complicated cascade". *Id.* at 194-95. Dr. Dreskin opined that in contrast, a flu vaccine administered in the arm would prompt the lymph nodes to mount an immune, specifically IgG, response. *Id.* at 195-96. "You educate the lymphocytes that would then be present to inactivate a virus during an actual

infection before it causes the respiratory epithelial damage." *Id.* at 196. Accordingly, Dr. Dreskin opined that flu vaccine cannot cause asthma exacerbation and that flu vaccine instead helps people with asthma who later contract live flu virus and can mount a more robust response. *Id.* at 196-98; *see also* Tr. 239-40 (cross-examination on this subject).

Dr. Dreskin agreed that "years ago", it was thought that individuals with egg allergies could develop allergic reactions upon receiving flu vaccines which contain egg protein. Tr. 189. He filed a 2010 publication by the Centers for Disease Control ("CDC"), which provides:

> Vaccine components rarely can cause allergic reactions, also called immediate hypersensitivity reactions, among certain recipients. Immediate hypersensitivity reactions are mediated by preformed immunoglobulin E (IgE) antibodies against a vaccine component and *usually occur within minutes to hours of exposure*. Symptoms of immediate hypersensitivity range from mild urticaria (hives) and angioedema to anaphylaxis. Anaphylaxis is a severe life-threatening reaction that involves multiple organ systems and can progress rapidly. Symptoms and signs of anaphylaxis can include but are not limited to generalized urticaria, wheezing, swelling of the mouth and throat, difficulty breathing, vomiting, hypotension, decreased level of consciousness and shock.

Fiore et al., Centers for Disease Control and Prevention, *Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP)*, 59 MMWR Recomm. Rep. (2010) [Resp. Ex. B14] at 20 (emphasis added). Another article co-authored by Dr. Dreskin provides that anaphylaxis can involve the skin and/or mucosa and respiratory compromise (such as constriction of the breathing passages, dyspnea, wheeze/bronchospasm, decreased peak expiratory flow, stridor, hypoxemia). Dreskin et al., *International Consensus (ICON): Allergic Reactions to Vaccines*, 9 World Allerg. J. 32 (2016), doi: 10.1186/s40413-016-0120-5 [Resp. Ex. B1] at 3.

In that 2010 publication, the CDC provided that allergic reactions might be caused by the vaccine antigen, residual animal protein, antimicrobial agents, preservatives, stabilizers, or other vaccine components. Ex. B14 at 21. One possible allergen is the residual egg protein present in flu vaccine. *Id.* The CDC recommended that individuals with a history of allergic reaction to egg protein should consult with a physician before receiving flu vaccine. *Id.*

Dr. Dreskin testified (in December 2017) that "a number of studies in the last five years" have reduced the thinking that flu vaccine can cause allergic reactions. *Id.* at 224. He filed literature corroborating these assertions. Notably, in 2012, a task force representing the American Academy of Allergy, Asthma, and Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology published an "Adverse Reactions to Vaccines Practice Parameter 2012 Update." Kelso et al., *Adverse Reactions to Vaccines Practice Parameter 2012 Update,* 130 J. Allergy Clin. Immunol. 25 (2012) [Resp. Ex. B9]. This publication went into more detail than the CDC publication cited above. This publication provides that anaphylaxis after vaccination is rare, estimated to occur at a rate of approximately 1 per million doses. Resp. Ex. B9 at 4. All suspected anaphylactic reactions to vaccines should be evaluated including through patient

history, skin test with vaccine and components (such as egg, gelatin, latex, and yeast), and measurement of IgE levels. *Id.* at 5. After the task force's original publication in January 2011, several additional studies concerning patients with egg allergies were completed. *Id.* at 12. A subsequent addendum provides:

> The areas of uncertainty in [the January 2011] original parameter stemmed from the fact that relatively few studies had investigated the safety of administering TIV [inactivated trivalent influenza vaccine] to patients with a history of a severe reaction to the ingestion of egg and concern about the amount of residual ovalbumin in some vaccines. Studies published in the past year offer further data supporting the safety of influenza vaccine in even patients with severe egg allergy and offer reassurance about the ovalbumin content of the vaccines.

Id. The addendum details seven studies (six published in 2010 – 2011) reporting on administration of inactivated flu vaccine to individuals with egg allergies that were either proven (e.g., by skin test) or known by history. A considerable majority received inactivated flu vaccine without any serious reactions. *Id.* at 12. "Of note, in those studies that included control subjects without egg allergy, similar rates of reactions between the 2 groups were reported, indicating that not all adverse reactions to influenza vaccination are related to egg allergy." *Id.* at 12-13 (including a table detailing the studies). Additionally, "Most studies on influenza vaccine in patients with egg allergy have specifically included patients with histories of anaphylaxis to egg ingestion… These patients with severe egg allergy have tolerated the vaccine without serious reactions, as is the case with patients with less severe egg allergy." *Id.* at 14. Accordingly, the task force – representing several academies of allergy, asthma, and immunology – recommended that patients with egg allergy should receive inactivated flu vaccine because the risks of vaccinating are outweighed by the risks of not vaccinating. *Id.* While the studies above did not support an association between inactivated flu vaccine and allergic reaction to egg, "those studies "cannot exclude a rare reaction" and there remains a "possibility of allergic reactions to any vaccination". *Id.* at 15. Accordingly, individuals with egg allergies should receive flu vaccine in a medical setting equipped to recognize and treat anaphylaxis, where they should remain for 30 minutes after vaccination. *Id.* Individuals with a history of only hives after egg ingestion can receive flu vaccine in a primary care provider's office, while individuals who have had more severe reactions (cardiovascular, respiratory, or gastrointestinal symptoms) should be in an allergist's office. *Id.*; *see also* Kelso et al., *Allergic Reactions after Immunization*, 110 Ann. Allerg. 397 (2013) [Resp. Ex. B10]; Tr. 189-90, 248-49. In a third article on the subject, the lead author, John M. Kelso, M.D., who is affiliated with the Scripps Institute, provides: "Can trivalent influenza vaccine safely be given to patients with asthma? [Answer:] TIV contains killed virus or viral subunits and cannot cause influenza. Further, the vaccine does not cause asthma exacerbations in children or adults with the disease." Kelso, *Safety of Influenza Vaccines*, 12 Curr. Opin. Allergy Clin. Immunol. 383 (2012) [Resp. Ex. B13] at 3.

In 2016, Dr. Kelso, Dr. Dreskin, and others authored an international consensus document on allergic reactions to vaccines. Dreskin et al., *International Consensus (ICON): Allergic Reactions to Vaccines*, 9 World Allerg. J. 32 (2016), doi: 10.1186/s40413-016-0120-5 [Resp. Ex. B1]. This publication also considers the possibility but notes the many different studies which did not find allergic reactions to egg protein in flu vaccine. *Id.* at 6-7. Vaccines

(including those against influenza) contain various other components in trace amounts, which are "usually insufficient to induce allergic reactions in most individuals with possible hypersensitivity to the component." *Id.* at 9-10. "However, individuals with unusually high levels of IgE antibody can theoretically react to very small amounts of these antigens and develop severe reactions, including anaphylaxis." *Id.* at 10. Kelso, Dreskin, et al. go on to provide "comprehensive and internationally accepted" resources "to help practitioners around the world" evaluate possible allergic reactions to vaccines, including flu. *Id.* at 16.

4. Conclusion Regarding *Loving* Prong Four (*Althen* Prong One)

Drs. Newmark and Dreskin agreed about the physiological changes that occur during an asthma exacerbation; that one asthma exacerbation increases the likelihood of further asthma exacerbations; and that some asthma exacerbations are allergic and IgE-mediated in nature. Dr. Newmark also opined that components of the flu vaccine – most likely egg protein – can cause allergic asthma exacerbation. Dr. Dreskin did not agree. Dr. Newmark filed a number of studies evaluating flu vaccine and asthma exacerbation. Certain of those studies suggested that flu vaccine was associated with a short-term decrease in expiratory flow, but not clinical symptoms. Those studies also did not suggest an allergic mechanism and tended to exclude participants with known allergies to egg, influenza protein, and other components of flu vaccine. Anand et al., Pet. Ex. 13(a); Nicholson et al., Pet. Ex. 13(c); Kmiecik et al., Pet. Ex. 13(e); Cates et al., Pet. Ex. 13(f); Ouellette et al., Pet. Ex. 13(h).

Dr. Dreskin showed that since approximately 2010, there have been a number of studies effectively testing Dr. Newmark's theory that an individual with an allergy to egg can have an allergic reaction to that component of flu vaccine. In these more recent studies, individuals with known egg allergies have received inactivated flu vaccine and tolerated it well. Dr. John Kelso at the Scripps Institute, who appears to be an influential authority on these subjects, specifically wrote that inactivated flu vaccine is safe for individuals with asthma and does not cause asthma exacerbations. Resp. Ex. B13 at 3.

The current consensus in the medical community seems to be that inactivated flu vaccine is generally not associated with allergic reactions even in individuals with known allergies. But because the studies to date cannot *exclude* the possibility of allergic reactions, individuals with known allergies should receive inactivated flu vaccine in a medical setting and should be observed for 30 minutes. Additionally, Dr. Dreskin opined that people with very high IgE levels may still have allergic reactions to vaccines, including flu.[22]

Accordingly, in this case, the evidence preponderates, if barely, in favor of petitioner's theory that rarely, an individual with an allergy to egg who receives flu vaccine can experience an allergic reaction. The allergic reaction can include the respiratory system to include airway constriction and mucus production, as seen in certain instances of anaphylaxis. That reaction can result in exacerbation of preexisting asthma, in an individual who has that condition.

[22] As discussed below under *Loving* prong five (*Althen* prong two), petitioner had normal or low general IgE levels, but was not tested for IgE specifically to egg.

However, it is also necessary to resolve whether this rare allergic reaction can manifest five to seven days later and whether it did occur in a petitioner without evidence of allergy with other possibly relevant factors at play. It is upon consideration of these factors, discussed below, that petitioner's claim fails.

E. *Loving* Prong Six (*Althen* Prong Three)

Althen prong three requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen* at 1281. That term has equated to the phrase, "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* at 1352.

1. Petitioner's Expert's Opinion Regarding *Loving* Prong Six (*Althen* Prong Three)

In this case, five days passed between the influenza vaccination on September 15, 2014 and the first manifestation of asthma exacerbation with scent sensitivity occurring on September 20, 2014. That was followed by the development of cough, which became severe and prompted petitioner to drive herself to the emergency room on September 22, 2014. She was given albuterol and prednisone, then discharged the same day. Then, on September 24, 2014, she returned to the emergency room and was hospitalized for six days for her asthma exacerbation. *See, e.g.*, Pet. Ex. 11 at 6; Tr. 110 (Dr. Newmark's statements endorsing a five-day onset); Resp. Ex. B at 5; Tr. 190 (Dr. Dreskin).

Petitioner's expert Dr. Newmark opined that this was an acceptable temporal association for an IgE-mediated allergic reaction to develop and then manifest as an asthma exacerbation. He allowed that allergic reactions causing anaphylaxis and respiratory compromise can often occur "immediately." Tr. 77-81. Dr. Newmark opined however, that not everyone reacts the same way to allergens. He opined that "the degree of inflammatory mediators in any given patient is going to be different." Tr. 82. In some individuals, the allergic reaction causes "more subtle changes that may take a few days to become apparent." In his clinical experience, he has seen "individuals with other types of allergen exposures where they don't have an immediate reaction but they have a more gradual onset of symptoms. And then on a certain point, they may have very – much more severe symptoms." Tr. 77-78; *see also id.* at 108-09.

Dr. Newmark also suggested that the allergic reaction can be less apparent, at first, in persons who are not "marathon runners" who avoid "pushing" themselves. Such an individual "can start to develop subtle changes in their airways and start to develop a little bit of airway edema and then kind of reach a critical mass where they get a lot worse on a particular day or in [petitioner's] case, over several days." Tr. 81-82.

In her post-hearing brief, petitioner avers: "By way of analogy, Dr. Newmark testified about his own relevant experience with asthma exacerbation. Dr. Newmark treats many World Trade Center ("WTC") first responders who now have asthma resulting from their exposure following the attack on the WTC." Pet. Post-Hearing Brief at 12. Petitioner avers: "The relevance of this particular group to our facts here relate to the spectrum of reactivity in asthmatics and specifically its sometimes more remote occurrence." *Id.* at 12-13, citing Tr. 103. While Dr. Newmark does have considerable experience treating WTC first responders who have developed asthma and other respiratory problems following exposure to various stimuli at the collapsed buildings, the relevance of that experience to this case was called into question later in the hearing, when I asked Dr. Newmark whether asthma is "always an IgE reaction." Tr. 82. He answered:

> Well, it's not always an IgE reaction. I mean, there are other types of reactions that you can see from mediator release, and not all asthma is allergic, in fact. There are other factors. *For instance, we've talked about the World Trade Center induced asthma. That's not an allergic-type asthma.* That's some other transformation that causes – other chemicals that cause mediator release.

Tr. 82-83 (emphasis added). Accordingly, Dr. Newmark's clinical experience in treating WTC first responders who developed asthma, while interesting and highly commendable, does not demonstrate that an *allergic, IgE-mediated* reaction can cause an asthma exacerbation first manifesting five days later.

Dr. Newmark opined that the timing in this case was also supported by his filed literature. Upon review, the webpage reporting asthma exacerbation after inactivated flu vaccine describes "*immediate*, presumably allergic reactions." Pet. Ex. 13(k) (emphasis added). Watson et al. considered possible allergic response to egg protein in flu vaccine, but did not address what timing would be acceptable. Pet. Ex. 13(d). Several other studies found an association between flu vaccination and increased bronchial reactivity, but not corresponding clinical symptoms. Moreover, those limited findings of bronchial reactivity generally were observed within the two or three days after vaccination. They either resolved or were not followed over time.

Dr. Newmark filed the study by Christy et al., which found an increased incidence of health utilization for asthma among vaccinated children compared to non-vaccinated children over the course of one year. Ex. 13(g). As discussed above, this study was retrospective, uncontrolled, lacking in detail, and the authors suspected that vaccination was simply a marker for bad asthma. Thus, this study does not support Dr. Newmark's opinion that flu vaccine can cause an allergic IgE-mediated allergic reaction that takes approximately five days to manifest.

Dr. Newmark cited Kmiecik et al. in support for the timing in this case. Tr. 149-50, referring to Pet. Ex. 13(e). Respondent's counsel asked: "Is this the only article that you discussed – or the only thing you discussed before today that would indicate a reaction [e.g., an allergic reaction to the flu vaccine] can occur five days later?" Tr. 150. Dr. Newmark answered: "I believe this is the one that specified that long a period." *Id.* However, Kmiecik et al. does not support that an allergic reaction can occur that much time after vaccination. They excluded a known allergy to any of the vaccine components, especially to egg or chicken protein. They did

not posit an allergic reaction. As Dr. Newmark acknowledged, Kmiecik et al. did not specify what specific types of reported events occurred within that 14-day time frame. *See* Tr. 151. Dr. Newmark also acknowledged that it was impossible to tell from the article whether the reported events were similar in nature to petitioner's case. *Id.* at 153. And finally, the study results were not particularly compelling, in the sense that participants had similar incidences of asthma exacerbation in the fourteen days following either flu vaccine or placebo. The results initially suggested a slightly higher incidence following flu vaccine. But upon further review, the authors observed that "[significantly more exacerbations occurred in each group during the first 14-day study period than during the second 14-day period… this result indicates that the sequence of vaccination was not likely to have affected the occurrence of an asthma exacerbation." *Id.* at 5. Thus, Kmiecik et al.'s eventual conclusion was that flu vaccine did not impact asthma exacerbation.

On cross-examination, Dr. Newmark agreed to respondent's counsel's statement that "on this record, there are no studies to show that the mechanism of IgE response manifesting four to five days later, there's nothing to suggest that on any of the articles filed." Tr. 154.

2. Respondent's Expert's Opinion Regarding *Loving* Prong Six (*Althen* Prong Three)

Dr. Dreskin opined that if a vaccine can cause an allergic asthma exacerbation, the medically acceptable time frame would be within four hours. Tr. 236-37. He opined that allergic asthma exacerbation is an IgE-mediated "immediate hypersensitivity reaction". This reaction is generally apparent within minutes but at maximum, within hours. Tr. 187-88, citing Dreskin, Kelso, et al., Resp. Ex. B1 at 2.

The literature supports that in "the majority of cases", anaphylaxis – the most severe form of IgE-mediated reactions – "occurs within minutes following an exposure to an allergen." Resp. Ex. B1 at 2. Various diagnostic criteria for anaphylaxis allow for onset within minutes to approximately four hours. *Id.*; Kelso et al., Resp. Ex. B9 at 5; Kelso, Resp. Ex. B10 at 2; CDC, Resp. Ex. B14 at 21.[23]

Certain rare IgE reactions can occur over a longer time frame. "Rarely, delayed-type hypersensitivity to a vaccine constituent (e.g., aluminum) may cause an injection site nodule, but this is not usually a contraindication to subsequent vaccination." Resp. Ex. B1 at 5. "Delayed anaphylaxis (onset 3 to 6 h after exposure) is a concept that has recently been well-described but in the context of individuals that have been bitten by the lone star tick and then develop IgE to a component of red meat… Of note, the route of exposure with red meat (ingestion) is different from the route of administration of vaccines (parenteral) and a delayed response due possibly to metabolic processes is more likely. Thus, vaccine-related allergic reactions including anaphylaxis should occur more quickly than seen in patients with allergy to red meat. Any vaccine-related reactions occurring more than 4 h[ours] after administration of a vaccine are

[23] Of note, the current Vaccine Injury Table (which is not effective for petitioner's claim, but is still instructive) creates a presumption of causation if influenza vaccine is followed within four hours by anaphylaxis meeting specific criteria. 42 C.F.R. §§ 100.3(a), (c)(1).

unlikely to be immediate hypersensitivity reactions.'" Resp. Ex. B-1 at 17, *see also* Resp. Ex. B at 5; Tr. 187-88 (in which Dr. Dreskin suggests that allergic reaction to red meat can take even longer to manifest, approximately 12 hours after vaccination).

Dr. Dreskin opined that an "IgE reaction that manifested with symptomatology… four to five days later" was "not compatible with our understanding of the pathophysiology of IgE-mediated reactions." Tr. 190. He opined that it was "not biologically plausible" for a "smoldering" IgE reaction to cause the first manifestation of mild symptoms in five days, escalating to more severe symptoms and presentation to the emergency room seven days after allergen exposure. *Id.* at 191. Dr. Dreskin stated that he was not aware of any medical literature postulating a "smoldering IgE reaction" to cause the type of symptoms seen in petitioner's case. Tr. 191-92.

Dr. Dreskin stated that in his clinical experience with patients with history of allergic reactions to antibiotics, the antibiotic can be administered in very gradual doses over a period of time, to allow a subclinical reaction resulting in desensitization and the elimination of further allergic reactions. Tr. 191. Accordingly, a "smoldering" or "very low-grade" IgE reaction "would actually result in desensitization." *Id.* at 190, 191.

Respondent's counsel asked: "Dr. Newmark testified that he has patients who he believes to have had a reaction to a flu vaccination in the same fact pattern as was in this case, [or at least a reaction] that was first clinically noticed in the time frame of this case. Have you found that to be your experience in your practice?" Tr. 219. Dr. Dreskin responded: "No." *Id.*

3. Conclusion Regarding *Loving* Prong Six (*Althen* Prong Three)

In this case, petitioner received a flu vaccine, developed the first manifestation of asthma exacerbation with scent sensitivity approximately five days thereafter, and developed worsening symptoms culminating in her presentation to the emergency room seven days after the flu vaccine. Her expert Dr. Newmark opined that this was an acceptable temporal association for a "smoldering" IgE-mediated allergic reaction, which he has seen in his clinical experience as a pulmonologist. Dr. Newmark's clinical experience is commendable. It does not seem unreasonable, in his clinical practice, to suspect that a patient has experienced an allergic reaction and to evaluate that further. However, Dr. Newmark did not provide any literature to support that the timing seen in this case is appropriate for an allergic IgE-mediated reaction. Respondent's expert Dr. Dreskin opined and filed literature supporting the proposition that an IgE-mediated reaction occurs within minutes to four hours of allergen exposure. Upon review, the available evidence does not support petitioner's position that the timing in this case is acceptable or consistent with her theory of an allergic reaction to the flu vaccine. Accordingly, petitioner has not established *Loving* prong six (*Althen* prong three).

F. *Loving* Prong Five (*Althen* Prong Two)

Under *Althen* prong two, petitioner must prove "a logical sequence of cause and effect showing that the vaccination was the reason for [her] injury." *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e. in this particular case, did the

vaccine(s) cause the alleged injury. Temporal association alone is not evidence of causation. *See Grant v. Sec'y of Health & Human Servs.,* 9556 F.2d 1144, 1148 (Fed. Cir. 1992). This sequence of cause and effect is usually supported by facts derived from petitioner's medical records. *Althen,* 418 F.3d at 1278; *Andreu,* 569 F.3d at 1375-77; *Capizzano,* 440 F.3d at 1326; *Grant,* 956 F.2d at 1148.

1. Petitioner's Expert's Opinion Regarding *Loving* Prong Five (*Althen* Prong Two)

Dr. Newmark opined that a person can have an exacerbation, not have any symptoms or require any treatment for "a period of years", then "be exposed to something that causes an exacerbation" which may be either limited or permanent. Tr. 68-69. In this case, petitioner was diagnosed with asthma in 1990 and she had an exacerbation in 2012. Tr. 70-71. Dr. Newmark opined that the 2012 exacerbation was "mild" because she didn't require "prolonged steroids", she was not "in and out of the emergency department", and she was not admitted to the hospital. Tr. 112. Within a year, her symptoms resolved. *Id.* A pulmonary function test in October 2012 was normal. Tr. at 71-72, citing Pet. Ex. 7 at 181-82. She ceased to seek medical attention and treatment. Tr. at 70-73. Accordingly, Dr. Newmark opined that petitioner's asthma was controlled, mild, and intermittent before the September 2014 flu vaccine. *See also* Tr. at 97.

Dr. Newmark opined that petitioner's September 2014 flu vaccine caused an asthma exacerbation. This was the first flu vaccine she had received in her life, which made her "more prone to have an acute… allergic reaction." Tr. at 101. Dr. Newmark opined that this was a "smoldering reaction that was not clinically apparent for the first few days, and then she wound up with a full-blown severe exacerbation." *Id.* at 101-02; *see also id.* at 103, 148-49, 154-55. He noted that beginning approximately five days after the flu vaccine: "[S]he had a couple of days where she wasn't feeling well. She was coughing." *Id.* at 109. Seven days after the flu vaccine, she went to the emergency room. *Id.*

Dr. Newmark opined that when a patient presents with an asthma exacerbation, his typical work up includes family history, the particular individual's history, compliance with medication and treatment, symptoms, and stimuli encountered around the time of the asthma exacerbation. *Id.* at 63-64. Dr. Newmark opined that each patient has particular asthma triggers. Possible triggers include viruses, plants, pollens, pet dander, foods, chemicals, bleach, smoke, cold air, exercise, and even emotional changes. Tr. 56-57, 69, 87. It is "essential" to identify the specific patient's asthma trigger(s), so that can be avoided going forward. *Id.* at 65-66.

If Dr. Newmark thoroughly interviews a patient who has experienced an asthma exacerbation, ruled out all other possible triggers in the prior fourteen days, and "the only thing left standing" is a flu vaccine, he would "warn the patient to never have [the flu vaccine] again." Tr. at 106; *see also id.* at 160. I asked whether Dr. Newmark had "seen this kind of response to the vaccine before". *Id.* He said yes, rarely, "a couple of times over the last 40 years." *Id.* On cross-examination, respondent's counsel asked why he hasn't published about these patients. *Id.* at 158-59. Dr. Newmark answered that he's "out taking care of patients all day." *Id.* at 159.

Dr. Newmark opined that the treating physicians conducted a thorough history. Tr. at 85-92 (discussing records from her initial hospitalization and from her primary care provider Dr. Daub). Dr. Newmark opined that the pulmonologist Dr. Mazza took a history "and the only reason he gives for the exacerbation of her asthma is a reaction to the influenza vaccine". Tr. 92-93 (discussing Ex. 7 at 101[24]). Dr. Newmark opined that Dr. Mazza was "fully versed in asthma" and was in fact "listed as an asthma specialist by the primary care doctor". Tr. 93-94.

Dr. Newmark testified that he typically tests the patient's total IgE antibody level, "which tells you whether this patient has had allergies at least up until that point". *Id.* at 64. He also tests the patient's IgE antibodies specific to particular allergens. *Id.* He usually does "respiratory allergens that include molds, grasses, dogs, cats. Sometimes if [he] thinks there's a food-related allergy, [he] might throw in… particular foods." *Id.* I asked whether the total IgE antibody level and specific IgE antibody levels are always consistent. *Id.* at 65. Dr. Newmark responded: "[Y]es and no. Sometimes you have a high IgE and none of the allergens you happen to test for show up. So there are many things that we can't test for and don't test for that still might cause an acute allergic reaction… the… converse… is sometimes you'll show up some mild reactivity to particular elements, dogs, cats, or whatever, and the total IgE is not elevated, meaning that it's probably not of clinical significance." *Id.*

In this case, Dr. Newmark testified that petitioner had an IgE-mediated allergic reaction to the ovalbumin (egg protein) in the flu vaccine:

> DR. NEWMARK: ... So there is some ovalbumin, and that may be the cause of an IgE or an allergic reaction.
> THE COURT: Which is what you think occurred here?
> DR. NEWMARK: Correct.
> THE COURT: And would a person typically test positive for an egg allergy if they would have had this kind of response to the ovalbumin?
> DR. NEWMARK: Yeah, I mean, I think they would. In this case, she was never – Ms. Green was never tested.
> THE COURT: For egg?
> DR. NEWMARK: Yeah, for egg allergy. People with egg allergies are at increased risk for developing reactions to the flu vaccine.

Tr. at 116.

Dr. Newmark opined: "Since no alternative causative agents were listed in the records, had Ms. Green not received the influenza vaccine, she would not have sustained any exacerbation of [her] asthma symptoms and very likely would have continued on her course of maintaining a stable and controlled asthma." Pet. Ex. 11 at 5; *see also* Tr. at 55-56, 97-98. He repeated: "… there has to be something, where you don't go from being well one day and no symptoms and normal pulmonary function to having severe exacerbation requiring high-dose

[24] During the entitlement hearing, petitioner's counsel directed Dr. Newmark to Pet. Ex. 4 at 93. That is a copy of the appointment record in question. However, this opinion cites to the complete set of pulmonology records, filed as Pet. Ex. 7, in which this particular appointment is at pages 101-03.

steroid and multiple nebulizers and having to give up working because you could barely function. That doesn't happen like that for no reason." Tr. at 114.

Dr. Newmark opined that the 2012 exacerbation was "likely caused by a respiratory infection" for which she received antibiotics. In contrast, there was no evidence of a respiratory infection in September 2014. Tr. at 86, 111-12. The primary care provider was aware of petitioner's sleep apnea, but did not suggest that condition was uncontrolled. Tr. 88-89. The primary care provider was also aware of her obesity, but did not suggest that could have been at fault for her asthma exacerbation. Tr. 88-89. On cross-examination, Dr. Newmark allowed that: "Obstructive sleep apnea may increase or worsen asthma in general." *Id.* at 159.

Dr. Newmark opined that petitioner's September 2014 asthma exacerbation increased her susceptibility for further exacerbations caused by various stimuli. Tr. at 97. This was "typical" and "a very common scenario that [Dr. Newmark] see[s] in the office. Tr. at 98; *see also* Tr. at 102, 110-11; *see also* Pet. Ex. 11 at 5; Pet. Ex. 14 at 3. Later in the testimony, Dr. Newmark put it slightly differently: "More likely if you have a *severe* exacerbation, you are prone to other *severe* exacerbations." Tr. at 113 (emphasis added); *see also id.* at 158.

2. Respondent's Expert's Opinion Regarding *Loving* Prong Five (*Althen* Prong Two)

Dr. Dreskin agreed that asthma exacerbations can be caused by a variety of stimuli, some of which are allergic and some of which are not allergic. Tr. 174-75, 238-39. Dr. Dreskin agreed that when a patient presents with an asthma exacerbation, he tries to discern what the stimulus might have been." *Id.* at 175. Dr. Dreskin added that it was "not uncommon" to fail to identify the stimulus. *Id.* at 175, 199.

On cross-examination, Dr. Dreskin opined that if a patient presented with a history of flu vaccine followed a few days later by asthma exacerbation, he would not readily withhold future flu vaccines. Tr. 232. He would rule out alternative factors. *Id.* He would evaluate whether the patient's asthma was uncontrolled. *Id.* To rule out an allergic IgE-mediated reaction, he would do skin testing. *Id.* He would also order bloodwork. *Id.* at 230. Then he might give the patient one-tenth of a dose of the vaccine, followed by a full dose, under observation. *Id.* at 232.

Dr. Dreskin opined that petitioner's 2012 exacerbation went on for months, but seemed "overall less severe in terms of its longer-term outcomes" than the September 2014 exacerbation. Tr. 177. On the other hand, 2012 was earlier and: "Exacerbations tend to get worse over time." *Id.* One asthma exacerbation increases susceptibility for further exacerbations. *Id.* at 186.

I asked Dr. Dreskin why past asthma exacerbation(s) predicts future asthma exacerbation(s), particularly when they are separated in time, like the two-year period in this case. Tr. 200. Dr. Dreskin opined that a lot of medical conditions are intermittent. *Id.* Her asthma may not have been "as well-controlled as she thought." *Id.* "Maybe there were some underlying issues. Sometimes people with respiratory compromise will limit their activity so they're asymptomatic… [I]f they had pulmonary function testing through that period, you may

have seen something that was not clinically evident or even symptomatic to the individual… We're really not sure why." *Id.* at 200-01.

Dr. Dreskin opined that petitioner did have an asthma exacerbation in September 2014, but the flu vaccine was more likely than not "irrelevant". Tr. 176. People with asthma, particularly when they're not on controller medication, experience exacerbations. *Id.* On cross-examination, he opined that if petitioner had been on the Advair controller medication between 2012 – 2014, the September 2014 exacerbation would not have happened. *Id.* at 243. But the exacerbation was "very similar to asthma exacerbations that happen all the time." *Id.* at 176.

Dr. Dreskin opined that exacerbations occur frequently in the fall. *Id.* at 176, 226. These are caused by both seasonal allergens and viral infections. He opined that pollens can cause an allergic reaction that is mediated by toll-like receptors and the innate immune system, which results in seasonal rhinitis. Tr. 226.

Dr. Dreskin agreed that the September 2014 exacerbation had a "gradual onset", but not that it represented a "smoldering IgE reaction." Tr. 224. He opined that petitioner was "not a highly allergic individual". *Id.* She had low IgE levels, both in general and specific to a number of common household and seasonal allergens. The specific IgE tests were "all in the less than detectable range except for one that barely was detectable to a common outdoor mold." *Id.* at 224-25, *citing* Pet. Ex. 7 at 28 (January 2013 IgE testing); *see also* Pet. Ex. 18 at 13 (July 2016 IgE testing).

On cross-examination, petitioner's counsel asked about the treating pulmonologist's assessment that petitioner had an allergic reaction to the flu shot. Dr. Dreskin responded that although petitioner testified that the pulmonologist took a detailed history, the *recorded* history was not detailed. Tr. 245-46. The recorded history did not specify the time frame or that petitioner was coughing for two days prior to going to the emergency room. *Id.* at 246. Dr. Dreskin also opined that "most pulmonologists", presumably including this individual, would not have "expertise in the immunology of vaccines and how they may affect the body." *Id.* The pulmonologist's recorded history and impression of an allergic reaction to the flu vaccine represented a "hypothesis". *Id.* at 247. That didn't "necessarily make it right." *Id.* at 248.

Dr. Dreskin noted that in addition to asthma, petitioner had obstructive sleep apnea ("OSA") and obesity, which are all interrelated conditions. A person with OSA does not get enough oxygen, particularly at night, which is associated with poorer health outcomes. Tr. at 178. Dr. Dreskin introduced an article which provided: "Treatment for OSA improves asthma outcomes, such as symptoms, bronchodilator use, peak flow rates, and quality of life." Teodorescu et al., *Association Between Asthma and Risk of Developing Obstructive Sleep Apnea*, 313 JAMA 156 (2015) [Resp. Ex. B4] at 2; *see also* Ex. B at 4; Tr. at 180-81.

Dr. Dreskin opined that obesity influences OSA: "The more weight one has, the more tissue one has in the body, particularly in the posterior airway… And the more tissue there is in the back of the airway, the less room there is for air." Tr. 179. He added that: "Obesity actually can increase general systemic inflammation. Tr. 182. He introduced an article that provided:

> In our quest for more specific phenotypes and endotypes, there seem to exist at least two distinct subtypes of asthma in the obese; these are as follows: (1) early-onset (younger than 12 years and seen in both sexes), atopic, eosinophilic asthma with elevated titers of IgE that is in fact complicated by obesity, and (2) late-onset, non-atopic, non-eosinophilic asthma that may be caused by obesity and found predominantly in middle-aged women; the latter is increasingly shaping up as a distinct inflammatory, non-eosinophilic endotype.

Puthalapattu et al., *Asthma and Obstructive Sleep Apnea: Clinical and Pathogenic Interactions*, 62 J. Investig. Med. 665 (2014) [Resp. Ex. B5] at 6; *see also* Resp. Ex. B at 4; Tr. 181-83. Dr. Dreskin opined that the second phenotype is more challenging to treat and new drugs are being developed. Tr. 183. Dr. Dreskin opined that petitioner had the second phenotype. *Id.* He noted that petitioner had at least two complete blood counts showing very low eosinophil levels. *Id.*, referencing Pet. Ex. 2 at 31 (September 2014 CBC showing eosinophils at 0.03 x 10(3)/mcL (compared to a normal reference range of 0.00 – 0.70 x 10(3)/mcL)); Pet. Ex. 2 at 117 (January 2015 CBC showing eosinophils at 0.27 x 10(3)/mcL). Dr. Dreskin allowed that prednisone can lower the eosinophil count. Tr. 185.

On cross-examination, Dr. Dreskin opined that the September 2014 exacerbation could have been caused by an allergic reaction to pollen (which he stated was not mediated by IgE, but by toll-like receptors). Tr. 242. Her sleep apnea and obesity were not the cause, but they made her "more susceptible to whatever else… may have caused" the September 2014 exacerbation. Tr. 242. When petitioner's counsel continued questioning about possible causes, Dr. Dreskin answered: "if I needed to find a cause… it seems like… with the cough for two days, that she had a subclinical viral infection would be my supposition as a cause." Tr. 242-43.

Dr. Dreskin tended to agree that the September 2014 exacerbation contributed to her subsequent exacerbations and the overall worsening of her asthma. Tr. 238. In addition to stating the general proposition that one exacerbation makes more likely further exacerbations, Dr. Dreskin opined that at the first hospital encounter, petitioner was "inadequately treated" with only "20 milligrams twice a day of prednisone. *Id.* at 186, 238. Therefore, she had "ongoing airway inflammation making her more sensitive over time." *Id.* at 238.

3. Conclusion Regarding *Loving* Prong Five (*Althen* Prong Two)

The experts agreed that petitioner's September 2014 asthma exacerbation was more severe than what she had previously experienced. The September 2014 event also contributed to her subsequent exacerbations and the substantial worsening (or "significant aggravation") of her asthma. The experts disagreed about the underlying cause, which is determinative to *Loving* prong five (*Althen* prong two).

Dr. Newmark opined that petitioner had an allergic IgE-mediated reaction to the flu vaccine. Even if this theory and the time frame were both accepted[25], there is not preponderant evidence for an allergic reaction to the flu vaccine in this case. The experts agreed that

[25] As discussed in the preceding sections, there is not preponderant evidence for this theory or for this time frame.

evaluation for a possible allergic reaction would include taking a history. Here, the medical records do not mention egg allergy and petitioner testified that she was not allergic to any specific foods. Tr. at 12. The experts also agreed that evaluation for a possible allergic reaction would include testing IgE levels generally and to specific allergies. Petitioner underwent this testing in January 2013, *see* Pet. Ex. 7 at 27-28, and again in July 2016, *see* Pet. Ex. 18 at 13, 18-19. Neither round of testing included IgE antibodies specific to egg (or other components of the flu vaccine). However, she had insignificant IgE levels generally as well as to many other specific allergens. Dr. Newmark suggested that the total IgE level was of clinical significance. Tr. 65. Consistent with this testimony, it would seem that a person could have a clinically significant allergy to a stimulus that was not specifically tested, but that person would likely have an elevated general IgE level. Here, petitioner's general IgE level was normal if not low. Dr. Dreskin also opined that petitioner's low IgE levels reduced the likelihood of an IgE-mediated reaction to the flu vaccine. Tr. 224-25. Dr. Newmark also suggested that petitioner had low eosinophils, which supported that her asthma was not allergic, but had a different etiology. Dr. Newmark suggested that petitioner's asthma was instead related to her obesity and sleep apnea.

Dr. Newmark also opined that the treating pulmonologist Dr. Mazza reasonably concluded that petitioner's September 2014 asthma exacerbation was caused by an allergic reaction to the flu vaccine. Upon subsequent review, that was indeed Dr. Mazza's conclusion. Ex. 7 at 101. But it is also true that this was Dr. Mazza's initial consult with petitioner on November 26, 2014, more than two months after the vaccination and the initial asthma exacerbation. Dr. Mazza's assessment stemmed from the history of present illness: "*She states* that she was doing well with her asthma *until September 15 when* she had an allergic reaction to the flu shot." Ex. 7 at 103 (emphasis added). Dr. Mazza was establishing his doctor-patient relationship with petitioner and was relying entirely on her history, of which he does not record much detail. Of note, it is not clear whether Dr. Mazza, in recording petitioner's report of an allergic reaction, was aware that the flu vaccine was *given* on September 15 and it took five days for the first symptoms to manifest. As discussed in the preceding section on *Loving* prong six (*Althen* prong three), an allergic reaction is generally manifests within minutes to hours, not the five days seen here. Additionally, Dr. Mazza made this record based on petitioner's history, before both he and the primary care physician ordered repeat IgE testing, which did not have significant findings. As this record appears to be based solely on petitioner's own history and not on any testing or evidence that Dr. Mazza considered the separation in time between the vaccination and the onset of petitioner's asthma exacerbation, I do not find this record to persuasively support that the flu vaccine caused petitioner to have an allergic reaction resulting in asthma exacerbation.

Accordingly, there is not preponderant evidence that petitioner *did* develop an allergic IgE-mediated reaction to the flu vaccine's egg protein (or other components). Accordingly, petitioner has not established *Loving* prong five (*Althen* prong two).

G. Alternative Cause

As discussed above, petitioner did not establish her prima facie case. Accordingly, the burden did not shift to respondent to prove an alternative cause for the significant worsening of petitioner's asthma.

IV. Conclusion

As noted above, the reliability of petitioner's theory rests in part in consideration of the evidence discussed in each of the *Althen* prongs. Her theory that in rare cases, flu vaccine can cause an allergic reaction, which can cause exacerbation of preexisting asthma, would seem to be generally sound, if less likely, with the highly purified vaccines currently in use.

However, the probability of such a reaction explaining the exacerbation that occurred in the petitioner appears much less likely when other factors specific to this case are considered. The notion that an allergic reaction can smolder for five to seven days and then suddenly cause a severe asthma exacerbation seems particularly unlikely when considered in light of the usual mechanics of an allergic reaction that typically occurs quickly after the exposure to the allergic stimulus.

Further, allergies can be tested. While the experts agreed that a particular allergic stimulus may be missed because it was not tested, neither petitioner's general IgE levels nor her IgE levels to the specific allergens that were tested were at all high. Petitioner was not tested for an egg allergy, but she testified that she has never had food allergies, which undermines the likelihood that she had an allergic reaction to the egg protein in the flu vaccine.

Finally, Dr. Dreskin opined that an allergic type asthma seemed unlikely in petitioner's case. He suggested that petitioner's asthma more resembled a late-onset, non-allergic, non-eosinophilic type that is associated with obesity and obstructive sleep apnea, both of which were present in her case. Both doctors agreed that asthma tends to have periodic exacerbations and Dr. Dreskin stressed that use of controller medication makes them much less likely. Unfortunately, petitioner was not regularly using her prescribed controller medications at the time of the asthma exacerbations at issue. Accordingly, petitioner has not established that the flu vaccine caused or significantly contributed to the significant aggravation of her asthma. Accordingly, her claim must be and is hereby **DISMISSED.** In the absence of a motion for review filed pursuant to RCFC Appendix B, the Clerk of the Court is directed to enter judgment forthwith.[26]

IT IS SO ORDERED.

s/ Thomas L. Gowen
Thomas L. Gowen
Special Master

[26] Entry of judgment is expedited by each party's filing notice renouncing the right to seek review. Vaccine Rule 11(a).